

BY DEVELOPING METHODS FOR ANALYZING THE GENETIC SEQUENCES OF PATIENTS WITH HIV, CHRISTINA RAMIREZ KITCHEN SHOWS SCIENTISTS HOW THE VIRUS EVOLVES OVER TIME AND WITH TREATMENT – INFORMATION THAT COULD SAVE LIVES.



Formulas for Success

Biostatistician Decodes DNA Patterns to Fight HIV

As scientific debuts go, it would be hard to top the splash made by Dr. Christina Ramirez Kitchen, whose first peer-reviewed publication was co-authored with a famous HIV/AIDS clinician – and generated considerable controversy.

In the mid-1990s, Ramirez Kitchen was pursuing a graduate degree in statistics at Caltech when her thesis adviser asked if she would be interested in participating in a study of HIV progression. The project involved working with the adviser's neighbor, Dr. Michael S. Gottlieb – the physician who, while at UCLA in 1981, published the first report describing cases of AIDS.

Now, amid reports from clinical trials that the introduction of protease inhibitors and highly active anti-retroviral therapy (HAART) was resulting in dramatic improvements in patients, Gottlieb, who was running a large HIV clinic, was looking for help in investigating why what he was seeing in his own practice seemed different from what he was reading about in the clinical trials. Ramirez Kitchen agreed to assist with the statistical analysis, working with Gottlieb and HIV researcher Scott Kitchen – her future husband.

It would be years before their findings would be accepted for publication.

Among the group's conclusions: The decrease immediately seen in HIV morbidity and mortality following the advent of HAART treatment was most likely transient, the result of a period of delayed disease progression. "We found that resistance was winning – that certain patients were still failing these HAART regimens," Ramirez Kitchen recalls. "It was so contrary to what had been reported that the journals didn't want to believe it at first. People were talking about HAART as a possible cure for HIV because of the good results in the clinical trials. But in the clinic, where there is a more diverse patient population and there

tends to be less compliance to the regimen, we were finding viral resistance.”

Although it took time, the results ultimately gained widespread acceptance in the scientific community, as did another element of the team’s findings: that a patient’s initial response to HAART is predictive of future clinical prognosis.

Ramirez Kitchen, who joined the UCLA School of Public Health faculty as an assistant professor of biostatistics in 2001, has been bringing her statistical expertise to HIV/AIDS studies ever since.

“It’s such an interesting problem,” she says. “At the time I started, protease inhibitors were new, HIV sequencing was new, and the virus and our perception of it were changing so much. It was an exciting time to become involved.”

Ramirez Kitchen has focused on how HIV mutates in response to the drugs used to treat it, the process by which the virus resists drug treatment, and its “fitness” – the Darwinian process by which the strains of the virus that survive attacks by drugs and the immune system and are able to replicate tend to be the strongest, making the next generation more fit and difficult to combat.

Many of these questions can be answered with molecular sequence data. Using DNA and RNA sequences, Ramirez Kitchen and Dr. Marc Suchard, an assistant professor of human genetics and biomathematics at UCLA, have developed a methodology enabling the simultaneous analysis of multiple sequences across multiple patients over a period of time. “We try to use these long strings of DNA components to make sense of what the virus is doing so that we might be able to outsmart it – to use its own ability to mutate against itself,” she explains.

“Prior methods didn’t allow for longitudinal observation, and that’s where things get interesting – studying how the virus evolves. We use our methods in an effort to translate what’s going on in the clinic so that we can better understand how the virus is affecting patients.”

Ramirez Kitchen is excited about her most recent studies and what they could ultimately mean for HIV patients who have not responded to HAART. Working with her husband, who is now a virologist at UCLA, and Dr. Jerome Zack, an immunologist and associate director of the UCLA AIDS Institute, she developed a statistical methodology to determine which protease mutations are most harmful to the virus, and confirmed its validity in a study with Zack’s SCID-hu mouse model of HIV. Now, Ramirez Kitchen is working with other UCLA colleagues in an effort to use that information to

devise an important new clinical strategy that would drive the virus into a less fit state. “We believe this could provide hope for patients in whom the virus has been resistant to treatment,” she says.

Another novel methodology helped Ramirez Kitchen make important discoveries about the virus and its response to HAART treatment. HIV typically has two types of co-receptors, CXCR4 and CCR5. Ramirez Kitchen’s group found that even when HAART fails to control the virus, it can still change it into a less pathogenic form by forcing it to switch from the CXCR4 co-receptor to the less-pathogenic CCR5 co-receptor. “We believe that’s one of the reasons that some patients who fail to respond to treatment still fare better if they stay on it,” Ramirez Kitchen explains. In particular, she says, for patients who express the CXCR4 phenotype, switching to CCR5 appears to lead to an improved clinical prognosis.

“The real importance of this work is the methodology that allows us to quantify the proportion of a patient’s virus that uses CXCR4 or CCR5,” Ramirez Kitchen says. “That is especially important to know with the advent of co-receptor specific therapy and entry inhibitors.” She and her colleagues subsequently obtained a patent on the methodology.

Ramirez Kitchen has long been drawn to using math as a way to solve important problems. “That’s probably why I’m a bit more applied than most biostatisticians,” she says. “I like to be able to ask a question and try to come up with an answer, especially as it relates back to the clinic.” Some of her most rewarding moments as a faculty member, she adds, occur when she can see the excited look in her students’ eyes as they realize through their research that the theoretical concepts they learned in the classroom can be used to help scientists and physicians understand clinical problems, and thus can make a difference in patients’ lives.

Ramirez Kitchen tells her students that one of the most important skills for biostatisticians is a strong understanding of the subject matter to which they’re applying their formulas. “As a statistician, you need to be able to develop new methodology that is appropriate for your data, implement that methodology and then translate it so that it’s understandable to the other scientists and clinicians,” she says. “To do that, it’s extremely helpful to have a good understanding of the biological system you’re working with. That way, you can bring more to the problem, and even help to initiate new inquiries.”

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